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Bio-Chips and Chips for Bio

**A Report Commissioned by the
MEDEA+ Scientific Committee**

MEDEA Working Group on Biochips & Chips in Bio

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Executive summary

Bio-microsystems represent a very large ensemble of devices encompassing miniaturized and integrated devices for biological/biochemical functions in research & development, diagnostics, therapy and monitoring. Devices are called, sometimes redundantly, biochips, bioMEMS, microarrays, DNA chips, Lab-On-Chips, Cell-Chips, micro implants, drug delivery systems (DDS), and μ TAS (micro Total Analysis Systems). Foreseeable applications are numerous and will be implemented on a large scale but without a clear definition of time as yet. Bio-microsystems deal with a field of major importance: healthcare is a primary economic activity and will continue to grow. Additionally, many sectors of healthcare will be impacted by bio-microsystems: diagnostics, drug development, adaptive drug treatment, health monitoring, transplants and implants (natural or artificial). A major change in healthcare practices can be foreseen from the occurrence of smart “lab on chip” for disposable point of care or home diagnostics. Other markets will also have sizeable needs of chips: the food industry will increasingly require real-time controls. Security and environmental issues are becoming major items on the political agenda.

Bio-microsystems bring speed, parallelism, complexity and redundancy, low cost, and integrated intelligence. These attributes are due to the massively parallel manufacturing of miniature systems allowed by microelectronics fabrication techniques. These unique characteristics, together with a significant number of unmet medical needs, make healthcare a major application area. The increasing sophistication in medical technology has also increased the associated costs, therefore technologies that can provide monitoring, diagnostics and therapeutics with high speed, high accuracy, and high disposability while at low cost, low invasiveness, and low supervision are bound to be quickly incorporated in the medical practice. Additionally other areas that require increasingly refined monitoring such as the food industry can equally benefit from those attributes.

Despite their great potential, bio-microsystems have historically thrived through limited, small-scale isolated successes, with no clear roadmap and no major application in sight within a finite time frame. Any policy to improve the competitive position of Europe requires an increase in solid collaboration between engineers and medical professionals; this could lead to developments of major medical significance and address challenges not yet explored (historically it is known that medical research partnerships have originated most of the successful bio-microsystems applications).

Europe has some of the biggest pharmaceutical and biomedical companies in the world, yet most of the bio-microsystem activity is still happening in the US. As a consequence, most of the present-day intellectual property generation is happening there, which will potentially block future European attempts to compensate for this delay. It is therefore imperative that we be proactive now to avoid such an irreversible situation in the future.

European microsystem research has typically been more systems orientated than that in the US or elsewhere, which could give European chip houses a competitive advantage as some of them are indeed ready to incorporate more non-conventional technologies. They also come with a history of successful packaging solutions, which represent a key effort in the development of bio-microsystems; no matter how novel and unique a device may be, it is usually the packaging and integration schemes that will ultimately gauge its success.

One might wonder why microelectronics companies should feel an urgency to act: there is no large-scale application in view (as is usually the case for emerging technologies in emerging markets, market studies are of no help to identify the future), the funding situation is bad in Europe (at variance with the massive infusion of US funds for bio-terrorism actions). We see two major reasons:

- Although one can not foresee a date for bio-MEMS becoming a major industry, it will happen somewhere in 10-20 years, as it will be a major technology allowing cost reduction of healthcare systems, already a dominant worldwide activity and growing at a fast pace.
- The importance of that business for microelectronics companies is not clear: will the bulk of the added value be in the bio layer? In any case, the past example of mobile telecommunication systems is clear-cut: the establishment of GSM as the European standard has allowed European manufacturers to become world leaders, with European chip makers having a major thrust from that situation. It was a win-win situation for everyone in Europe.

Therefore, it is in the interest of every European company to have Europe at the best level in the bio-MEMS industry. For that, it is essential that companies (including those in microelectronics, biotech, pharmaceuticals, etc) be brought together with medical centres and healthcare authorities in general to implement specific programs that will facilitate joint work, regulatory compliance, and intellectual property management. MEDEA+ can have the unique role of promoting urgent action in Europe, possibly launching its own program in bio-microsystems. It can create a sister organization – MEDEA Life – that would specifically deal with the topic, with added strength coming from the participation of the medical community at large as well as biotech and pharmaceutical companies.

Recommendations for actions

1. Definition of a roadmap towards the creation of a competitive bio-microsystems industry.

In view of the many issues involved in industry development in *bio-microsystems* (technological, standardisation, mix of bio and microtechnologies, regulations, testing, medical validation, etc), one needs to act concurrently to solve these in due time. Creating the roadmap will allow to waste no time, and could give Europe an edge to enter the markets when they appear.

Recommendation: industries (microelectronics and biotech) should get together with researchers, doctors, people from the healthcare system (hospitals, Health organisations, etc..) and social security, with the help of the Commission, in order to create a roadmap that would lead towards the development of the bio-microsystems technology base and to their implementation in the various areas.

2. Creation of a "MEDEA Life", association of industries (microelectronics, biotech, pharmaceutical), medics, researchers, government, healthcare organizations, to launch initiatives to ready Europe in the bio-microsystem business.

MEDEA has shown the impact of a coordinated proposal force by industries. A similar association is needed in the bio-microsystem field to get the right actions implemented at the right level. It will allow acting on IP issues and differences in the approach peculiarities of each involved field such as pharmaceutical and medical. It will also promote the association of professionals from all the different backgrounds and guide them towards specific actions for the implementation of their ideas.

Recommendation : Create a MEDEA Life. It will benefit from the participation of current MEDEA+ members and its creation can be inserted as part of the second phase of MEDEA+, due to start in 2005.

3. Creation of programs targeted at implementing new technologies in the healthcare systems, through e.g. pilot programs at the European level.

A close collaboration with the medical community is essential during the development of new systems and also at the application phase. Additionally, the nature of the healthcare system in European countries is such that typically it does not promote the introduction of new technologies based on cost alternatives, as opposed to what happens in the US. Establishing pilot programs will facilitate this process.

Recommendation: establish pilot user projects at the European level for the development and application of bio-microsystems and evaluation of their cost effectiveness in the healthcare systems. Develop industry through end-user-led pilot programs (similar to MEDEA actions).

4. Create mechanisms for facilitating regulation compliance by participating enterprises

Regulations play a major role for new healthcare technologies. The sheer complexity of the certification process can be detrimental to the development of new technologies. A specific project can provide regulatory support and directly assist in the reduction in the time to market. Simultaneously, MEDEA Life should promote a unified regulatory system within Europe.

Recommendation: provide support for fast regulation compliance and promote a unified European regulatory system

5. Creation of a unified European healthcare technology base

The fragmentation of the European healthcare technology market requires action towards unification, taking into account the national aspects of healthcare systems.

Recommendation: beyond creating pilot implementation programs and acting on regulations, actions should be conducted towards the creation of a European healthcare technology market.

6. Implementation in the FP6 calls of targeted areas on bio-microsystems to:

- **support new concepts in technology**
- **promote the partnering between medics and engineers**
- **contemplate unmet medical needs**
- **develop portability of biological applications on bio-microsystem platforms**

Having itemized bio-microsystems in various parts of the first two calls of FP6 blurred the funding possibilities of bio-microsystems. Having them compete for funding against applications in very different fields does not ensure a fair evaluation process in broad expert panels. Having a single funding source will ensure good competition and good balance between the various actions to be undertaken.

Recommendation: establish specialized calls in FP6 for bio-microsystems. Make specific calls for SMEs in the field to develop their participation at the right level.

7. Stimulate education programs in the field of bio-microsystems.

The broad multidisciplinary skills required for biochips have to be developed through a variety of new education actions, at various levels of the education system. Interdisciplinary education programs, workshops etc. are to be combined with interdisciplinary funding schemes.

Recommendation: establish educational programs, at the European level when necessary, to develop the technologies and use of bio-microsystems.

8. Action #1 for MEDEA+: promote the creation of a sister organisation “MEDEA life” to take care of the field.

Given MEDEA’s strong experience in organizing industries and its interests in the promotion of bio-microsystems activities in Europe – well in phase with its own programs – MEDEA+ could act in helping to bring to existence an industry-led organization specialized in biochips, comprising the main actors in the biotech and microelectronics areas. A first step could be to have the three main companies contact the major biotech players in Europe to act as a nucleus for the future organization.

Recommendation: establish a MEDEA-like organization focused on bio-microsystems.

9. Action #2 for MEDEA+: promote European actions in the field of bio-microsystems.

In a first phase, before MEDEA life exists, MEDEA+ could promote the need for increased European actions in the field of bio-microsystems. This could consist in bringing the importance and needs of the bio-microsystems field to the attention of various policy makers at the European level.

Recommendation: publicize the issues in the bio-microsystems field with policy makers.

10. Action #3 for MEDEA+: Launch a series of specific programs on bio-microsystems.

The bio-microsystem activity fits well into the application-driven areas of MEDEA+ activities. Given the importance and timeliness of increased activity in Europe, MEDEA+ could launch specific programs on biochips, defined by a team of experts, without waiting for the creation of its sister organisation.

Recommendation: launch specific MEDEA+ programs based on bio-microsystems.

Summary of the MEDEA+ Workshop “Bio-Chips and Chips for Bio” Leuven (B), 4th June 2004

On the 4th of June 2004, a workshop was held in Leuven with the objective of disseminating the conclusions of the Working Group of the MEDEA+ Scientific Committee, thus allowing the discussion of their findings before a broader audience and consequently the fine-tuning of their recommendations. Attendance consisted of approximately seventy senior scientists and managers from industry, consortia and authorities from Europe. The event consisted of a series of selected talks, followed by a panel discussion.

Workshop chair: Prof. Roger De Keersmaecker, Vice President Strategic Relations, IMEC, Belgium.

Panel moderator: Dr. Herc Neves, BioMEMS Principal Scientist, IMEC, Belgium.

Keynote speaker: Prof. Marc Madou, University of California in Irvine, USA.

Speakers:

- Dr. Olivier Elsenhans, Head of Technology Management, Diagnostics Division, Roche Instrument Centre, Switzerland;
- Anton Hofmeister, General Manager, Microfluidics Division, STMicroelectronics, Italy;
- Dr. Staf Van Reet, Vice-President, Johnson & Johnson Development Corporation, Belgium;
- Richard Walker, Principal Consultant, Quintiles Transnational, UK;
- Prof. Claude Weisbuch, Laboratory PMC, Ecole Polytechnique, France, and Distinguished Professor, Materials Department, University of California at Santa Barbara, USA.

Panellists:

The above listed speakers, plus:

- Dr. Torik Ayoubi, Supervisor, Transcription Profiling Unit, Genome Centre Maastricht, The Netherlands;
- Dr. Marc Waer, Medical Director, University Hospitals, University of Leuven, Belgium.

Statement summary

Education

We need to improve the close interaction between the engineering and biomedical communities, especially through the education system. Faculties should be more interdisciplinary, with joint appointments and dual advisors for graduate students. We should adapt existing educational programmes and create new ones at training centres at various levels. We should also promote pre-competitive collaborations.

The medical school concept – driven by a wish to integrate university tasks and health economics – is threatening the integration between medical sciences and other fields; possible solutions include the adoption of multidisciplinary grants and funding and multidisciplinary training (such as the MD-PhD programs created in the USA). Biomedical engineering programs may not suffice to bridge the gap, since it is important that the individuals involved

in this task be also present in the clinical environment. Another important aspect that transcends the education issue is that the whole professional framework is too rigid for interdisciplinary individuals; for instance, it is very difficult to create interdisciplinary grants.

Knowledge

Complementary partnerships between technology providers and technology users in the life sciences and IVD markets should be promoted. Biomedical applications should be validated by the biomedical professional in close collaboration with their microsystems colleagues. We should work towards changing the general negative perception associated with DNA testing and better inform the end user of technological benefits such as faster and better diagnostics. Specific targeted programs are needed, preferably set by academic centres in conjunction with industries.

Business

Even if bio-microsystems do not become mainstream in the near future, they have the potential for playing a predominant role in selected applications; there are very significant drivers such as the need for a large amount of assays. The genomic revolution is a powerful example; hundreds of genes have already been found to be associated with genetic disorders that include some major diseases. It is important to invest in applications that can act as technology drivers and to translate technology into advantages to the end user.

It is essential to focus R&D on the clinical content rather than just what is technologically feasible. Additionally, global regulatory and reimbursement issues should be addressed at the earliest stages of product development. One should also understand that developing clinical acceptance and achieving routine use takes a long time – often as long as R&D – and that performance and quality issues tend to dominate. It is important to be proactive in defining the regulatory/quality environment, using a high standard that is integrated for internal use.

Cheap, disposable silicon-based bio-microsystems can be realised, but their integration still remains a problem.

Policies

Europe-wide institutions should be created to provide uniform rules and financial support. European governments and VCs should be convinced to keep investing at a higher level than the US to catch up; Europe should increase investment at universities, provide start-up capital to translate basic research into clinical applications and create dedicated incubators in proximity to academic hospitals.

We should lobby for regulatory interpretation in Europe, with industrial views by the organisations.

Interaction between the different players should most definitely be stimulated, and for this the creation of MEDEA Life can be an excellent vehicle. Many isolated initiatives have taken place with little coordination, and MEDEA Life can offer the much needed structure. Even with initial tensions, the various organisations active in the bio field should come together. This will facilitate the approximation with the IC industry, which so far has been hesitant to enter the field because of uncertain business expectations. A major concern, however, is

whether MEDEA Life will gather enough critical mass to be established; related areas such as health instrumentation, environmental and food industries should also be considered. Furthermore, other associations and organisations have already been devoted to the life sciences and have generated their own roadmaps, such as EURIMUS and NEXUS; the specific mission of MEDEA Life has to be defined with that in mind. Roadmap activities are still needed, but the endeavour is complex; it can however be funded under FP6.

The creation of a unified European technology base is a broader issue that applies to many aspects of healthcare. To a large extent this remains a nationally regulated sector, subject to European rules and regulations.

The creation of new programmes at the European level can only succeed with the full commitment of partners and clear IP agreements. However, the academic partners are often taking the lead and industry is playing a secondary role. To be really productive, clear exploitation plans should be put forward.

1. Introduction & synthetic view

In the last 20 years, there has been a great effort in biology, chemistry, and engineering to pursue the advantages of miniaturization for cheaper, better, faster devices in the life sciences such as bio-microsystems, which encompass a variety of devices, depending on the technology used or the targeted application. So far, some of the most relevant applications have included the acceleration of DNA amplification and detection and other molecular analyses from pre-processed samples. To attain the pervasiveness enjoyed today by electronic devices, a much higher degree of functional integration will be required, to address the new goal of sample-to-answer systems. Analytical methods are critical in a wide range of industry sectors, from pharmaceutical research to the food industry, from environmental control to diagnostics, to name a few. In the last ten years, the field of laboratory methods for biology and chemistry has been shaken by a revolution that is reshaping the way research and analyses are carried out.

Today, most of the uses occur in research labs, relying on microarrays of various types. The main activity is for DNA analysis (DNA chips) or protein analysis, for instance through antigen-antibody recognition for diagnostics purpose or drug screening (protein chips).

Advantages are very similar to those obtained from the silicon integrated circuit: one immediately obtains massive parallelism in measurements, as well as the possibility to carry out many experiments under exactly similar conditions, a situation which improves reliability in a field intrinsically prone to experimental uncertainties. Thus, chips with the full human genome have recently been achieved, which shows the degree of parallelism reached. Then, DNA microarrays allow screening a single sample of DNA for hundreds of mutations in parallel. Using at the same time DNA probes from different samples (for instance from healthy or sick person), one can make a differential mapping of the gene interactions with the probe genetic material. Multiple technologies are presently used, the dominant ones being the fluorescence detection of tagged molecules in microarrays (with up to a hundreds of thousands of spotted species) or the microwell plates allowing hundreds of reactions to take place simultaneously.

The specific advantages that can be achieved using microtechnologies are related to a few general points:

Parallelism. As it has been learned from the microelectronic industry, miniaturization can lead to massive parallelism. The need to carry out reactions in a parallel fashion, e.g. for screening compounds of potential pharmaceutical activities, has progressively led to the development of standard plates with an increasing number of smaller and smaller reaction wells, as a substitute for the classical test tubes (microwell plates or microplates). The major driving force for miniaturization has been the need to increase parallelism, in the rush to discover genomic information.

As explained before, different technologies have been proposed for implementing DNA arrays. For example, *Affymetrix* can address more than 500,000 test sites on its photolithographic in-situ synthesis devices, whereby *Cartesian Technologies* can address less than 100,000 test sites with printing technology based devices. Direct light-driven *in-situ* synthesis devices proposed by *Febit* allow realizing approximately 50,000 test sites per chip. The *Combimatrix* approach, which allows on-chip synthesis as well but based on an electronic principle, provides a few thousands of test sites per chip. *Nanogen* chips, which are operated on the basis of electronic-based site addressing to control immobilization of predefined probe molecules, offer a few hundred probe sites on a single device.

However, at this point, it has to be emphasized that the required parallelism does not directly translate into the requirement to always realize the maximally achievable number of test sites on a given platform. The required number of test sites and test to be performed in parallel on a chip, respectively, strongly depends on the application.

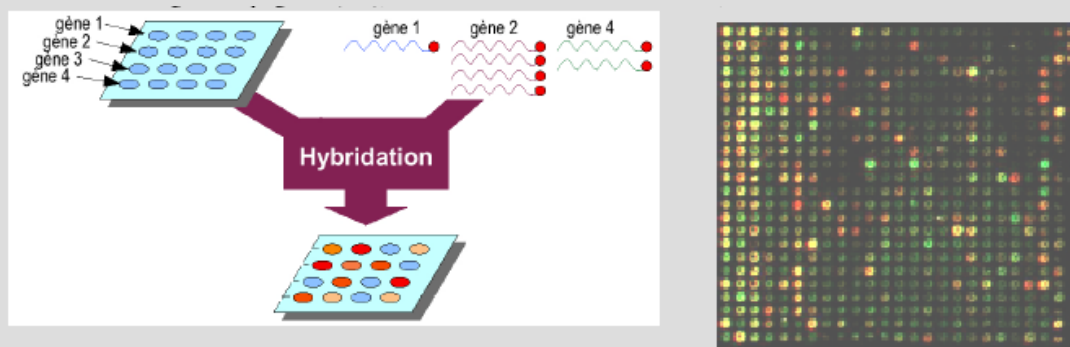
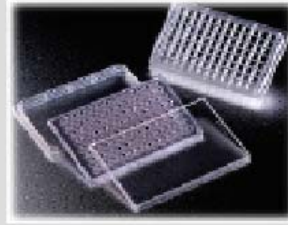


Figure 1: Schematics of a gene chip. Genes 1 through 4, which are labeled with fluorescent molecules, are associated with spotted genes on a glass slide. After hybridization between the spotted (probes) and unknown (targets) genes, the slide is scanned in a fluorescence microscope to detect the attachment spots, which reveal the nature of the target genes.

Reduced reagent consumption. Another major benefit of miniaturization is the cost reduction for screening the compound libraries, which pharmaceutical companies systematically test to establish their potential activity in a given cell-biology problem. For decades, test tubes, small flasks of glass with a volume of a few *ml*, have been the standard tools for handling biochemical samples. These compounds are often very expensive and reducing the volume of the reaction vessel of orders of magnitude was immediately perceived as an important benefit. As example, microtiter plates (or microwell plates), used for combinatorial chemistry in drug discovery and for a large number of biology protocols, are implemented in the standards of 96, 384, and 1536 *wells*, whose volume is 10 μl , 25 μl , and 5 μl , respectively. *Caliper sipper chips* can handle few nanoliters per well with up to 100,000-fold reduction compared to 96-plates in target use for high throughput screenings.

Figure 2: Microtiter (microwell) plates.



Speed/throughput. It turns out that shrinking dimensions not only can improve the above performance parameters, but it has additional advantages which are bound to the physics of the experiment itself, when heat or mass transfer are involved, as illustrated in the table. As an example, DNA amplification by PCR requires the cycling of the sample through three different temperatures (denaturation at above 90°C, annealing at 50-60°C, depending on the primers, and extension at 72°C). In this case, smaller volumes lead to faster heating and cooling cycles, thus shortening the time to accomplish the required number of cycles (20-40), from several hours to few minutes. Similarly, for miniaturized molecular assays, smaller dimensions help reduce the incubation time due to the fact that diffusion of molecules on a microscopic scale is achieved in a shorter time. On the other hand, since laminar flow dominates at very small geometries, mixing should be achieved predominantly by diffusion.

Volume	1 μ L	1nL	1pL	1fL
<i>Cube size</i>	1mm	100μm	10μm	1μm
<i>Diffusion time</i>	500s	5s	0.05s	0.5ms

Functional Integration. Although the above points are important, the most exciting opportunity from miniaturization will be in functional integration, which will allow one to quickly and cheaply perform complex multi-step analytical protocols, which traditionally require a host of different machines. This will be similar to what microelectronics brought to the computer industry, which evolved from large, expensive mainframes to cheap, ubiquitous personal computers with an exponential increase in computing power at affordable costs. For microelectronics, the reduction in cost and the increase in capabilities translated to a pervasive deployment of the technology, which is why today we have electronic devices not only in computers, but also in washing machines, toys, post-cards, cell phones, etc. So why should this not happen to lab-on-a-chip platforms? To continue the parallel with computer industry, we can assess where we stand now with a reference to the form factor scale. Traditional analytical techniques could fit in a room (like the early mainframes). The disruptive technology of ICs led to the PC era of desktop systems, which fit on a table. The lab-on-a-chip approach can be imagined as the IC equivalent in analytical laboratories. Although some of the early lab-on-a-chip products currently available are actually bench top instruments, one cannot say we are already at the PC equivalent stage. The key missing features are functional integration and the general-purpose capability.

The driving forces behind this evolution today are the high throughput screening (HTS) for genomic research and the drug discovery in the pharmaceutical industry. This has resulted in a multitude of DNA array chip companies in the late nineties. Typical DNA array technology consists of a desktop

instrument with disposable cartridges. The cartridges contain arrays of hundreds of thousands of elements to which are attached single stranded DNA molecules. Microfluidic channels on top of the array allow the transfer of the DNA samples under test to the desired spots on the array where hybridisation has to take place. Detection is typically optical, based on fluorescent labels.

Lab-on-a-Chip is a transcending concept, which should revolutionize multiple areas in biotechnology. The term is used to describe miniaturized, integrated platforms for complex chemical and biological reactions. Its future in biomedical research is increasingly based on the ability to manipulate molecules within microfluidic chips and devices, and the capacity to integrate these new tools with powerful informatics capabilities and high throughput automation.

Over the last years, three evolutions are taking place: more functional integration, the shift from DNA detection to protein detection and the spill over of technology into other application domains downstream of HTS.

- More functional integration is needed in order to go from sample to answer systems. The US military, through its funding agency DARPA, is funding fully integrated portable systems that can detect airborne pathogens such as anthrax and smallpox. This requires the integration of sample preparation systems with a compact sensing system together with a data analysis platform. It is the search for functional integration in sample preparation that is driving the research in microfluidic systems.
- The interest in protein detection stems from the fact that proteins are the actual molecules that are directly linked to our well being. The major challenge is that there are far more proteins than genes and that protein functionality is strongly related to its three dimensional shape. Typical proteomics systems bind some form of antibodies to a chip surface. The antibodies strongly react with the substance under test if the matching antigen is present after which optical (ELISA, SPR) or mass spectrometry detection follows.
- The high investments in HTS are driving the evolution of bio-microsystems. However, once new technologies become more mature for HTS they often find their way in more niche markets. Examples are the POC systems for cardiac failure and cancer detection. These systems reuse the HTS protein based detection technologies to a large extent, but optimise the system for cost and speed of the assay instead of throughput.

At this stage, there is no clear winning technology. All manufacturers use different sample preparations, surface chemistries and detection principles (though most of them are optical). Patents and intellectual property are very important assets for all of them. This results in many multi million dollar litigations and lawsuits. Most companies have a direct or indirect link to a pharmaceutical group that is funding and driving the research. Most of the companies are still in the R&D phase and are not making any profit. A lot of the companies seem to work with a business model similar to what we know as joint development programs. They install the equipment on site of a pharmaceutical company at a minimal cost. During this phase they have a co-development to get the equipment fully developed.

Overall, the bio-microsystem market is a very competitive market which requires a high investment (cumulative deficits on the order of \$100M). The high investment costs combined with the huge potential of the bio-microsystem technologies will probably give rise to a lot of M&As over the next years.

We mainly discussed above the way to the diagnostics lab on chip, where most of the activity and results occur today. Also, it is the main activity of the participants in the working group. However, one should not forget the wide-ranging applications of microsystems in other areas, such as drug delivery systems, and implants of many sorts, which will be addressed below.

2. Overview of application domains

2.1 Chips in diagnostics and therapeutic devices

The development of molecular biology and genomics has altered *in-vitro* diagnosis and opened up immense possibilities for early and personalized diagnosis. A new revolution is in preparation in the health industry, equivalent to the switch to digital technology.

The “DNA chip” tool, a result of genome work at the beginning of the 1990s, has a powerful diagnosis potential, particularly in the field of infectious diseases, due to the accuracy and speed at which it is able to identify in detail pathogens and their possible resistance to antibiotic and antiviral treatments. It is also of great interest for genetic diagnosis and gene expression monitoring diagnosis.

However, wide distribution of molecular diagnosis methods depends on the possibility of reducing test costs considerably and making information available within a very short time. The ultimate point of care requirement is to be able to undertake medical diagnostic with the minimum number of interventions, in a technology that demonstrates extremely high specificity with the possibility of detection at low concentration and with overall regulatory compliance.

As in the digital field, micro and nanotechnologies provide the tools for this molecular diagnosis innovation. This is possible because they offer the possibility of miniaturizing molecular biology tests within a lab-on-chip, capable of performing a whole biological protocol. This miniaturization offers fundamental advantages for cost reduction, such as collective manufacture at wafer level, smaller reagent quantities and parallelism, enabling significant improvement of analysis output and reducing the delay in obtaining results.

Firstly, we will use micro-systems technology for the advantages offered by these devices in terms of speed and size. The small volumes utilized by these devices enable us to imagine production of closed consumables incorporating all the reagents required for the tests, and preventing all flows from filtering outside the consumable. Moreover, the low weight and small distances involved enable considerable acceleration of the analysis process. Finally, when mass-produced, these micro-systems can offer low production costs with the silicon part placed in a plastic card, containing and delivering the reagents required for the test.

The development of these key functions needs a multi disciplinary approach where technologists, engineers and biologists are closely working together, especially at interface level. New technologies have to be developed to improve the overall design, to increase the speed of analysis, to reduce sample size.

2.2 Microsystems for healthcare

Numerous applications make use of sensors and actuator systems in and around the body. In the figure below we have classified the different applications according to their application domain (medical vs. entertainment, comfort sport) and their placement (inside vs. outside the body).

The pacemaker is based on an implantable electric pulse generator that delivers electric stimuli to the heart. Current products combine the generator with programmable features. A combination of miniaturized electric sensors, acceleration sensors, position sensors and minute ventilation sensors monitor the patient's activity and the complete system determines and applies the appropriate pacing rate. To date, almost 1 million of these devices have been implanted.

The cochlear implant is a device that can stimulate the auditory nerve of profoundly deaf people. It picks up the sound via an external microphone. The sound is analysed and digitised and the resulting

stimuli are sent through the skull via an inductive link to the implant. The implant performs further data processing and stimulates 22 electrodes that are curled into the cochlea. In the current implementation the speech processor can be placed behind the ear. It weighs 11g and provides 20 to 50 hours autonomy.

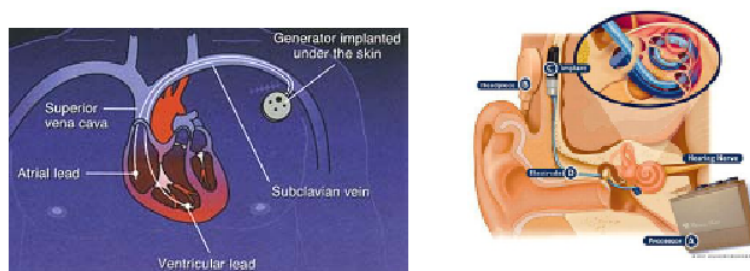


Figure 3: The cardiac pacemaker and the cochlear implant.

Technology for diabetes is one of the key drivers for drug delivery systems and wireless implantable microsystems. With 5% of the world population older than 20 affected by diabetes the possible economic return and social impact is enormous. Implantable insulin pumps have been commercially introduced by Minimed recently. The pump itself is a microdevice with a very precise flow activated by a remote control. The device also contains an insulin reservoir of 15ml that has to be replaced every two to three months. It can run on a single primary battery for about 10 years. In parallel, many companies and research institutes are investigating implantable blood glucose monitors. Prototypes are currently being tested in lab conditions. The major challenge seems to be to create a sensing mechanism which is accurate and reliable enough and does not trigger a reaction by the immune system. It is expected that it will take another 5 to 10 years before these devices will be available to patients.

Also for sports and infotainment, we see a number of new devices on the market these days. Good examples are the speed/distance watches marketed by Nike and Timex. Nike makes use of advanced accelerometer based pedometer technology from Dynastream. Timex makes use of a traditional GPS receiver from Garmin. Bodymedia is marketing a device that measures acceleration, heat flux, galvanic skin response and near-body ambient temperature. Based on these measurements it computes information on the wearer's caloric consumption, sleep onset or sleep duration. This may be a solution waiting for a problem, but the company is claiming that its technology can be used for collecting contextual data allowing to determine whether someone is sleeping or laying down or doing exercises.

The broad technology goals of these device manufacturers can be summarized as follows:

To increase the functionality of the devices for diagnostics and therapeutics and eventually integrate them into closed-loop theranostics systems.

To reduce the cost of the devices and the associated services.

To improve convenience for users.

However, manufacturers are facing quite of a few challenges on their way to these goals.

Devices are battery powered. This limits the lifetime of the product and creates toxic waste for the environment. Especially for implantable products the limited battery capacity can be a major drawback. Some neurostimulation devices only last for six months after which a new operation is required to replace the battery.

Most systems work in standalone mode and have little or no interaction with other sensors or actuators. Networking the sensors and actuators will open up the door to new applications such as

multi-parameter biometrics and closed-loop chronic disease management functions, e.g. the combination of implantable glucose sensor and insulin pump can create an artificial pancreas function.

Giving the devices the possibility to talk to each other will also require making them more intelligent. Specific communication protocols and data supervision will be required.

Once systems become more complex, integration becomes a key bottleneck. Different heterogeneous components such as fluidic biosensors, radios, microprocessors and batteries will have to be integrated, in a small form factor, in a cost-efficient and reliable way.

Many of the challenges are medical. Today, it is often not well understood how we can measure and quantify certain phenomena or how we can link measurements to a certain pathology. Additionally, it is vital that devices should incorporate biocompatibility (which will prevent the triggering of an immune system response), biostability (which will ensure that the device will not be detrimentally affected by the harsh environment posed by the human body), and should be designed so as to prevent biofouling (the build-up of organic material such as proteins or fibrous tissue that will impair device performance).

Furthermore, there are also some societal challenges. Will society accept this kind of invasive technology?

2.3 Microelectronics in implanted prostheses

Some biomedical devices for implantation into the body use silicon microelectronic devices; others employ microfabrication technology to create structures that can interact with the body and mediate the process of healing.

The normal response of the body to an alien object is inflammation of the region around the implant and/or the sealing of the object from the rest of the body by surrounding it in fibrous tissue. The mechanical properties of the alien object are important in determining this strength of this response; in general a hard object (e.g. a silicon chip) will cause more inflammation than a thin sheet of organic polymer.

Nerve cells communicate using electrical signals and these signals can be detected inside the body using arrays of microelectrodes or FETs. With the neurons involved in motor functions, the coding (or meaning) of the nervous signals is understood partially; however this is not at all true of the signals in the brain or elsewhere in the central nervous system (CNS). Indeed the understanding of the how the brain functions is one of the greatest intellectual challenges to mankind; progress can only be expected relatively slowly.

However in the next twenty years, active electronic devices in or very close to the body and interacting with the nervous system, can be expected to bring relief to patients with loss of hearing (the first implants are in place), with blindness (much progress is being made on artificial retinas) and in the restoration of function of limbs after spinal injury. Direct communication to the CNS will await an understanding of how the brain works.

Tissue repair is beginning to be used in medical practice. For replacement skin, preparations using re-grown cells are already available. Rejection of alien cells by the immune system limits the choice of the source of cells for re-growth. The probability of rejection is very low with the patient's own cells, higher with cells from other humans and very high with cells from other animals. Present techniques extract cells from a patient, multiply them outside the body in a culture medium, and then seed them onto suitable scaffolds - usually biodegradable (polymeric) meshes. These are then implanted to give new tissue.

The challenge to be met in the formation of a complex organ (no-one has attempted this yet) is to combine all the necessary cell types and to provide vascularisation channels for blood and to enervate

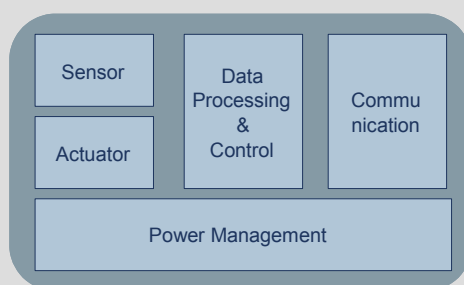
the construct with neurons. Present scaffolds are meshes of random holes; in life cells are exquisitely organised spatially.

The fabrication of scaffolds that show spatial organisation and allow properly for blood flow and nervous function is a true challenge for micro and nanofabrication techniques. A biodegradable material is essential, as no trace of the construct should be left after healing.

The involvement of the microelectronics industry in tissue engineering is required minimally at the level of the manufacture of the die used to shape the biodegradable scaffold (probably by mould injection). Physically the scaffold is much like packaging and some IC manufacturers also design and make their own packaging; therefore the role of the microfabrication industry could be much larger than just the dies.

2.4 An extreme technology vision for the year 2020

The figure below shows a technology vision for the year 2020. People will be carrying their personal body area network. This network can provide medical, sports or entertainment functions. The network consists of small sensor/actuator nodes, shown in the figure below. Each node has its own energy supply consisting of storage and scavenging devices. This supply is sufficient to make the device autonomous for the lifetime of the product or that of the user. Each node has enough intelligence on board to carry out its task. This can range from store and forward algorithms to complex non-linear multi parameter data analysis. Each node also carries a bi-directional radio, which allows it to communicate with other sensor nodes or with a body worn central node. The central node can be a dedicated device or it can be integrated into a watch, a PDA or a cell phone to allow it to communicate with the outside world. For this contact it will make use of standard telecommunication infrastructure such as WLAN, cellular phone or a standard telephone. These devices are in contact with the network that allows delivering services to the person using the body area network. Services can include checking the parameters of your gym workout, home monitoring of people by a nurse or medical doctor, and ambulatory monitoring of patients.



3. Enabling technologies for bio-microsystems

The development of molecular biology and genomics has altered *in-vitro* diagnosis and opened up immense possibilities for early and personalized diagnosis. Biomolecular diagnostics is a system problem. The development of fully integrated point-of-care medical diagnosis requires the miniaturization of several functional steps that are used today to perform a biological analysis in a laboratory:

- sample collection
- sample preparation

- amplification & sample analysis
- detection

The development of these key functions needs a multidisciplinary approach where technologists, engineers, biologists and medics are closely working together, especially at the interface level.

Such platforms are at the interface between the micro and nano worlds, exploiting system integration of the key enabling technologies. These systems should offer greater user flexibility through the incorporation of novel transducer configurations, organic surface chemistry and optimised biochemical probes, all integrated in a durable, simple and cheap package. To achieve this vision, two main key areas must be investigated: the development of an adequate biosensor interface based on self-assembled monolayers and the development of novel transducers based on microelectronic technology.

3.1 Detection technology

Today most DNA chips utilize fluorescence markers. Associated with fluorescence confocal scanners, this technology achieves remarkable performance in terms of sensitivity and accuracy. However, these standards might not apply to future protein chips. The array chemistry will be completely different and primarily based on the type of protein ligands that will be selected and also on the assay format that will be used. But proteomics technology is still at its infancy, so the development of direct measurement of protein-protein interaction will be key to the competitiveness in this area.

One of the actively researched technologies concentrates in the electrical readout, based on implementation of electrical signal generation and electronic detection integrated using CMOS technology. Various other types of biosensor transducers are currently being developed and have reached different stages of maturity (see figures below). A common theme in the evaluation of these transducer systems should be the focus on the direct detection of targeted bio-species without the incorporation of biomolecular labelling. As an example, the coupling of magnetic labels to biomolecules can provide interesting perspectives for realizing novel diagnostic chips. Under the influence of magnetic gradients on chip, the labels can be manipulated to direct the attached biomolecules to the chip surface or specific locations on chip. The presence of the magnetic labels can be detected, enabling to monitor for instance hybridisation results. The technique appears to be very sensitive and to reach very low detection limits. Targeted applications are mainly in the area of point-of-care detection for medical diagnostics. Typical examples in this area are the detection of cardiac markers, stroke markers and of prostate specific antigen (a marker for prostate cancer). The major challenge associated with label-free detection is the requirement of a low background even in the presence of large number of other molecules (this is also a problem with labelled detection, but it is reduced by the use of specific label attachment chemistry).

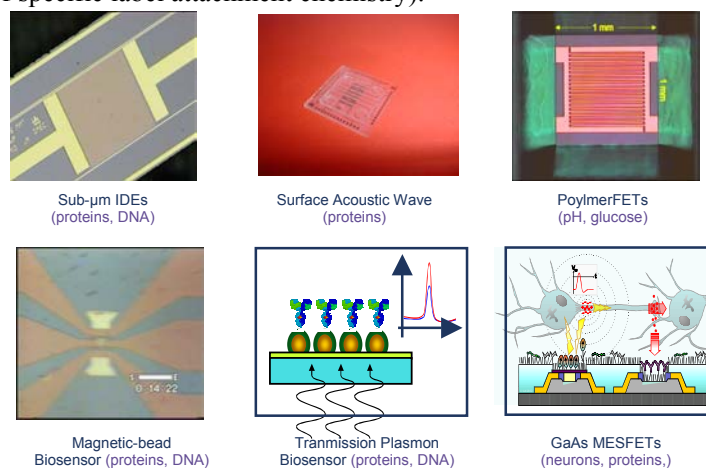


Figure 4: Different bio-transducer types (IMEC).

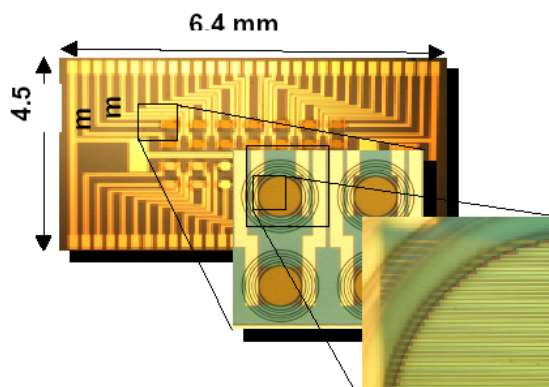


Figure 5: Electrochemical detection system (ISIT Fraunhofer).



Figure 6: Amperometric detection system (Motorola).

3.2 Microfluidics and microfluidic devices

Microfluidics is typically used to manipulate small volumes of liquids. Microfluidic devices use microfabrication technology to create structures and microchannels on different substrates such as plastics, glass or silicon. The technology is complicated by the modular nature of biological protocols, which are typically divided into subtasks that need to be coupled together and also require interfacing with the macro world for the injection and disposal of fluids.

Microfluidic systems miniaturize chemical and biological processes on a submillimeter scale. Reducing the dimensions of macroscopic biological or chemical laboratories is advantageous, as the small scale allows for the integration of various processes on one chip analogous to integrated microelectronic circuits. Also, the required reagent volumes are reduced, which saves material costs and allows the reactions to be carried out at high sample concentrations. These high concentrations drive the reactions towards the product side and accelerate the kinetics. Finally, miniaturization results in enhanced precision by providing homogenous reaction conditions.

Several approaches to realize microfluidic systems have been reported in the literature. In most cases the reagents are moved in channels or capillaries with typical diameters ranging from $50\mu\text{m}$ to $500\mu\text{m}$. These channels can be fabricated by deep etching processes on appropriate substrates such as glass, quartz or silicon. Alternatively, hot embossing is used to pattern polymer substrates. The channels are capped by anodic bonding or glue processes. Generally, these systems do not allow the reagents to be handled separately, as the channels need to be completely filled in order for the fluidics to work properly. Therefore, the application of these systems is restricted to continuous flow processes rather than batch processes as normally done in macroscopic laboratories.

Multiple pumping mechanisms are employed in microfluidics. Some pumping units are not an integral part of the chip and must be linked with appropriate tubes or pipes. They use principles such as piezoelectric actuation or mechanically moving parts to drive the reagents through the channels. Others take advantage of the small dimensions of the microfluidic channel itself. As the chemical

potentials of the channel walls and the liquid inside differ considerably, a space charge region forms at the interface. A voltage applied along the channel induces a flow at the space charge region that drags along the liquid closer to the centre of the channel. This electrokinetic effect works only for narrow channels and relatively high voltages. Fluidic motion can also be induced by spatially modulating the wetting properties of a substrate. For aqueous solutions, this can be achieved by patterning the substrate with hydrophobic and hydrophilic regions. The techniques used to realize such a modulation of the wetting properties include microcontact printing, vapour deposition, and photolithography. Aqueous solutions prefer to cover hydrophilic regions and avoid hydrophobic areas. Guided flow can be achieved by changing the wetting properties with time. For example, illumination can induce guided motion of liquids as the free energy of the surface changes locally under illumination. Other pumping mechanisms include peristaltic pumps based on thin membranes, or polymer films with a controlled deformation creating guided flow along microchannels.

A novel approach for miniaturized liquid handling that does not move the reagents in channels but rather on the surface of piezoelectric substrates has been introduced by Advantix. In this case interdigitated transducers excite surface acoustic waves (SAW) which transfer momentum to liquids placed on the chip. The reagents can be manipulated either as discrete droplets or by streaming patterns induced in macroscopic volumes. The technology allows both batch and continuous processes to be carried out at high speed. The most important feature, however, is the programmability of the chip as different assay protocols can be realized with the same chip layout.

3. 3. Lab on chip

In the past ten years there has been an increased interest in research on so-called Micro Total Analysis Systems (μ TAS) or Labs-on-a-Chip (LOC) as illustrated by the rapid growth of the international μ TAS conference, the appearance of an entirely new journal (*Lab-on-a-Chip*), a special section on this topic in the *Sensors and Actuators* journal, and many articles appearing in related journals (*Electrophoresis*, *Journal of Chromatography A*, *Analytical Chemistry*). Initially, there were two approaches followed in this field: one aiming at combining microsensors with fluidic components (pumps, flow sensors) into systems (e.g. ammonia/phosphate sensing); the other, which had a much greater impact, focused on miniaturization of analytical chemical methods, in particular separations, which after the first demonstration with amino acids led to an emphasis on genetic (DNA) analysis. As genetic analysis has now become a more or less routine method, the new focus has been for some time on using μ TAS systems for protein analysis. In addition, in the past few years, the interest in analysis of even more complex biological systems such as living cells with the use of microfabricated structures has attracted increased attention. Thus, the application of microfabrication techniques has really entered the life science field and has started to serve as a driving force for discovery in cell biology, neurobiology, pharmacology and tissue engineering.

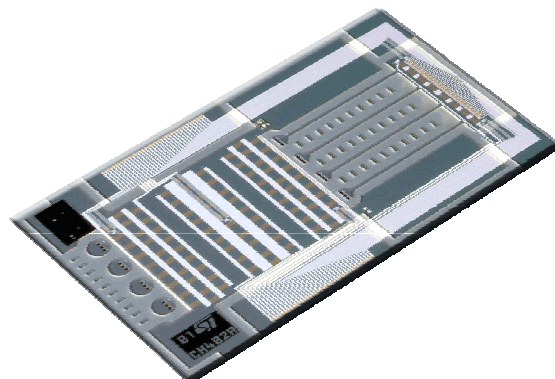


Figure 7: Integrated lab-on-chip (ST Microelectronics – LETI).

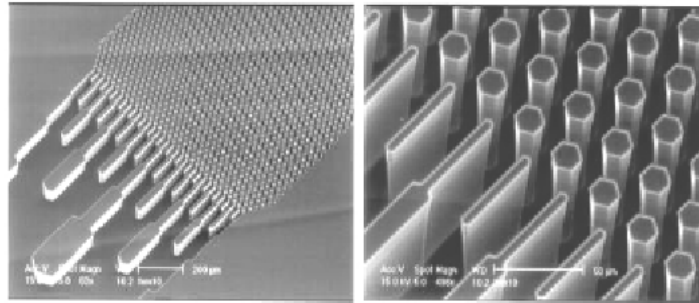


Figure 8: Biochip lab (Sanofi-Synthelabo)

3.4 Cellomics

Cellomics is the study of the temporal and spatial interrelations of cellular components, associated with genomic and proteomic information. Microfluidics is of particular importance to cellomics for several reasons:

- increased interest in biochemical experimentation/analysis of living single cells e.g. for studying effects of drugs, external stimuli on cell behaviour etc;
- possibility of easy integration of all kinds of analytical standard operations into microfluidic systems;
- several methods for manipulating large numbers of cells simultaneously can be used in microfluidic systems;
- the size of cells fits very well with that of commonly used fluidic devices (10-100 μm) and they can be individually manipulated;
- heat and mass transfer are improved in the microscale, and stronger electric fields can be attained at reduced voltages.

As the field of cellomics is expected to become a very important one, there is great interest to investigate what can be obtained with microfluidic devices and systems for analysis of living cells.

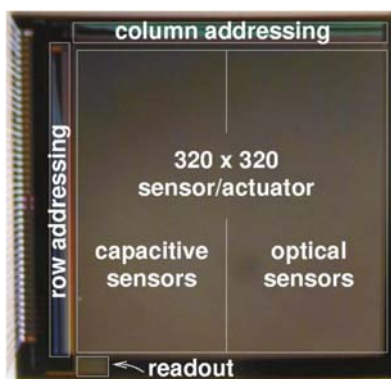


Figure 9: Chip for cell manipulation: up to 10k cells can be individually manipulated by dielectrophoretic forces for drug screening and rare cell analysis (0.35 mm technology; ARCES, University of Bologna).

3.5 Surface chemistry for bio-microsystems

One of the first technical challenges for bio-microsystems is the fixation of a molecule of interest (DNA, protein) on a solid surface. This immobilization has to be spatially precise (with micron size accuracy) and has to preserve the chemical activity of the molecule. The compatibility of the process with subsequent steps of the manufacturing process is also required.

The development of bio-microsystems is hampered by the insufficient stability and reproducibility of the interface between the bio-microsystem surface and the biological affinity elements. In addition, the increasing miniaturization of transducers (and of spot densities in microarrays) and the need for a higher sensitivity put more severe demands on the process of coupling biomolecules to bio-microsystem surfaces. Therefore, controlled thin film structures have to be developed, which allow the bio-affinity elements to be arranged and addressed in reproducible and controlled geometric surroundings.

Various techniques have been used to achieve these chemical-binding layers, such as liquid or vapour phase deposition. A large number of molecular species can be used, depending on the application requirements. The two most important and desired properties of any bio-microsystem are its specificity and its sensitivity towards the target analyte(s). The specificity of a bio-microsystem is entirely governed by the properties of the biological receptor component, since the analyte interacts with the bio-microsystem via these bioreceptors. The sensitivity of the integrated device, however, is dependent on both the biological component and the transducer. Indeed, in order to result in a high sensitivity, there must be a significant bioreceptor-analyte interaction and a high efficiency of the subsequent detection of this interaction by the transducer. The intrinsically high specificity of biomolecules and biological systems can be successfully exploited for the realization of highly sensitive bio-microsystems only if there is a highly efficient coupling between the biological and transducer components. Therefore, the bioreceptor molecules, e.g. DNA probes & antibodies, should be bound (or immobilized) on the surface in such a way that a significant and specific interaction with the target molecules occurs. Moreover, a well-defined interface between the biomolecules and the bio-microsystem surface would allow control over the reproducibility of the full bio-microsystem and over the extent of non-specific adsorption of any undesired bio species.

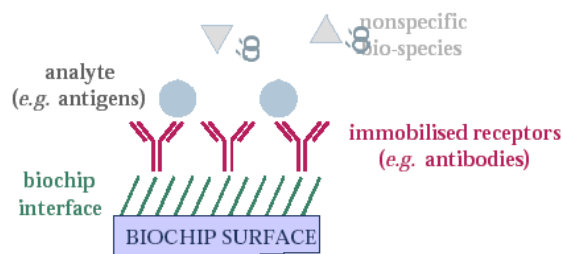


Figure 10: Idealized schematic presentation of a well-defined interface between the biological receptor molecules and the biochip surface.

3.6 Structured surfaces for implants

The cells in an animal are arranged in distinct patterns; their orientation and alignment depend on the purpose of the tissue. For example, in a tendon the cells are aligned in the direction of the cylindrical axis, thus producing a fibre-like structure that allows control of movement of articulated parts (as in a finger). In the development of the adult animal from the egg cues are given to the proliferating cells that dictate their final position, shape and orientation. In nature these cues can take the form of chemical gradients or chemical pathways as in the presence of adhesion promoting proteins or they can be purely physical – the response of cells to the topography of their surroundings. An understanding of the cues that influence cell positioning and alignment is crucial for cell and tissue engineering. If tissue is to be repaired, the new cells must be aligned and positioned correctly. The reconstruction of organs is even more demanding; here cells of different types have to be positioned correctly with respect to each other, and the whole composite of tissue specific cells, blood vessels, connective tissue and sensory cells (including nerve cells) all have to work correctly together. The issues in organ reconstruction clearly extend way beyond 2-dimensional cell patterning; without proper control at this basic level adequate reconstruction might not be achieved, therefore positional control of cells is an essential first step.

The general line of approach towards tissue reconstruction uses templates for structured growth. Cells isolated from a patient can, under the correct circumstances, be isolated, grown, and multiplied in culture. Such cells can then be seeded upon a suitable template, and put in a bio-reactor until the construct has matured. This construct can then be implanted back into the patient. Ideally the new implanted tissue should be indistinguishable from natural, undamaged tissue, and so the template material should be biodegradable such that it is slowly degrading within the body without leaving any remnants or releasing undesirable products of degradation. Polymeric materials that satisfy this specification include poly-ε-caprolactone or poly-L-lactic acid, which are widely used at present and easily available.

The patterning of the template to organise the cells can use chemical or physical cues, or probably ideally a combination of the two. Chemical patterning involves selectively cell adhesion to the template, while physical patterning confers topographical features to the template that favour or not cell attachment. Some of the most useful patterning methods utilize mechanical transfer, which encompasses methods such as nano-imprinting, nano-embossing and micro-contact patterning.

4. Markets, business issues, development issues, European issues. Industrial and research funding issues, in Europe

4.1 Bio-microsystem markets

Bio-microsystems market definition

The definition of bio-microsystems can vary broadly depending on platforms, operation principles, applications, etc. For the purpose of this document, we will assume the definition of bio-microsystems as *miniaturized and integrated devices which are used as a tool for biological and biochemical detection, analysis and actuation for use in various applications: research and development, diagnostic, therapy as well as health care monitoring, environment, defence, agriculture businesses*. Under the term bio-microsystems, we include devices currently defined as biosensors, micro-arrays, DNA chips, lab on chips, cell chips, bioMEMS, and more recently micro total analysis systems (μTAS).

Market segmentation

General

Bio-microsystems can be segmented according to:

- their technological characteristics (incorporation of microfluidics, integrated sensing, etc)
- the type of biological element studied (DNA, protein, cell, tissue)
- the application/function and final use (chronic monitoring, one-time testing)
- the final end user (pharmaceutical, agriculture, cosmetics, etc)

Market segments targeted by bio-microsystems	Market volume
<i>In-vitro</i> Diagnostics (IVD) (Genetic or Biochemical tests) such as Point of Care (POC) portable devices for: • Clinical Diag.: Glucose & lipid, Immunoassays, Microbiology, Virology • Forensic Medicine • Veterinary Dg • Agro-industrial testing (microbiology, GMO & allergen detection, IP enforcement) • Environmental testing (air, water pollutants: metals, chemicals, pathogens)	All IVD = 22B\$* • Glucose Diag. 5B\$ • Cancer Diag. 1.6B\$ • Cardiac Diag. 1.4B\$ Genetic IVD 0.66B\$ <i>(Clinica Reports 2001)</i>
Med. devices (Diagnostic and Therapy Equipment) such as: • Medical Imaging: e.g. <i>in-vivo</i> cameras	155 B\$

- Monitoring equipment - Implantable and portable devices	
High performance analysis systems for biology R&D (pharmaceutical, agricultural and academic) - Drug development - Gene profiling - Proteomics	14 B\$ (<i>Drug & Market Dev</i>) 0.6 B\$ (<i>2002</i>) 0.56 B\$ <i>Frontline (2000)</i>
Public Security / Defence / Substance Abuse	0.5B\$ (<i>CTST 2003</i>) but huge investments in R&D promoting all technological aspects, from microfabrication technologies to integrated systems.

For the purpose of this note, which aims to give growth perspective, we will divide the market based on final targeted application as follows:

- In-vitro* diagnostics as a potential replacement for conventional biologic (genetic, immunoassays, cellular) and biochemical tests. These tests are used today for instance to diagnose diabetes through glucose detection.
- In-vivo* diagnostics and therapy. These bio-microsystems will target the large market of Medical Devices that includes implants, surgical apparatus but also medical consumables such as dressings.
- Biological R&D applications conducted by academic research institutes as well as industries such as pharmaceutical.

The segment of public security (such as bio-terrorism countermeasures) and defence monitoring is considered separately because of its specific requirements and market.

The market of bio-microsystems in 2003 was still embryonic and very concentrated around the applications related to biological R&D; applications related to *in-vitro* diagnostics were emerging in 2003.

To put the markets (2002) in perspective, these are the individual worldwide shares:

Medical devices: \$170B

IVD market: \$19B

- Glucose sensors \$5B (annual growth >10%)
- Array \$50M (annual growth >10%)

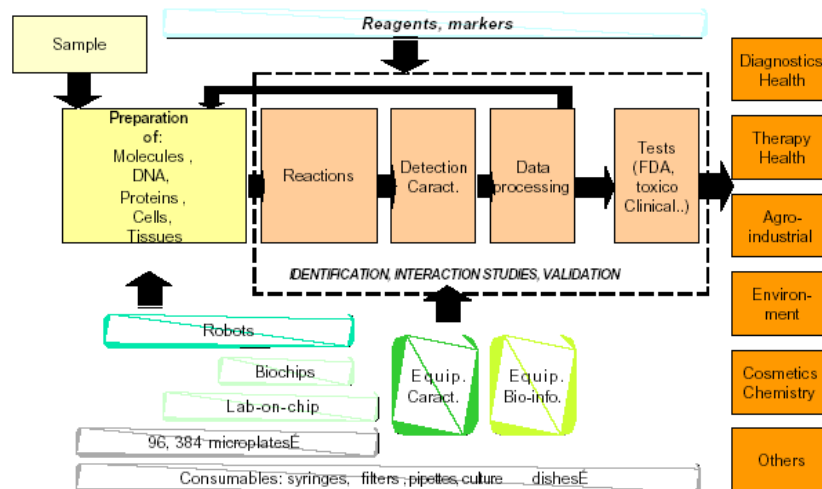
Active devices:

- Pacemakers \$5B
- Drug delivery \$3B

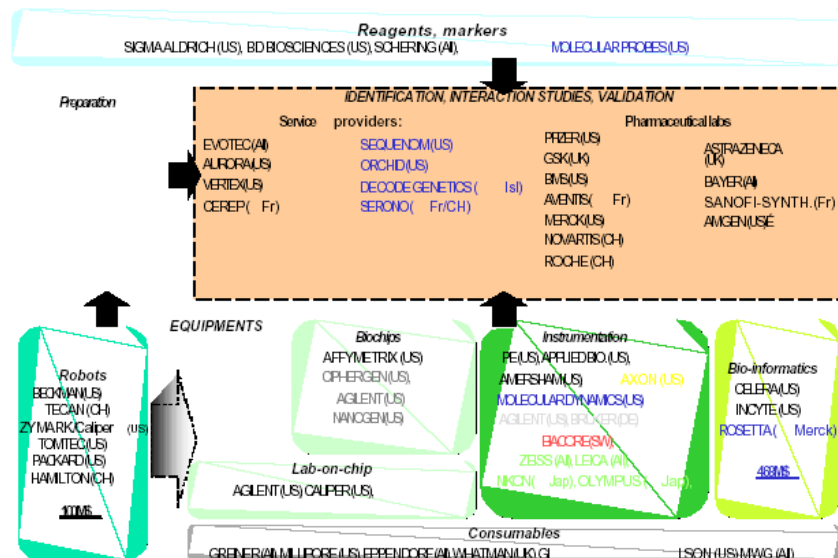
Biological R&D

We will now consider bio-microsystems used for the R&D application and verify which type of technological solutions they propose to replace and which suppliers in the chain are then involved. Bio-microsystems are targeting the whole biological process mainly for their added value of high throughput, miniaturization, automation and portability.

The various steps in traditional biological processes are described in the graph below. It highlights the various technological options utilised but also indicates that the R&D targets end users from different types of industry (pharmaceutical, agro-industrial, environmental, cosmetics).



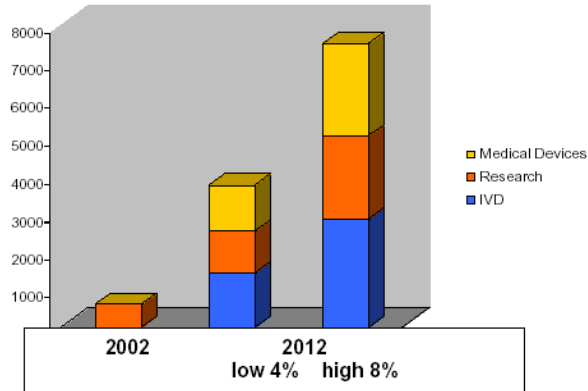
Along this biological process we have very different suppliers (from robotic platform manufacturers to plastic pipettes manufacturers). The graph below presents the suppliers at the different steps of the biological process. We have classified them according to their core activity (for example, Tecan appears under the robot segment even if it also proposes detection instrumentation). Companies such as pharmaceutical industries are involved at 2 levels in the process: they are considered for their own R&D but also as potential users/sellers of drugs developed by this process. *A remarkable feature appearing clearly in the table is the strength of big pharmaceutical companies in Europe, and the absence of Europe from the new bio-microsystem technologies, mainly represented by startups in the US.*



Market size and main actors

The bio-microsystems market in 2002 is mostly a biosensors market (devices without extensive micro fluidic devices) and includes products that are mainly used for R&D applications. It is estimated to **620 Millions of Dollars** by recapturing the sales of major actors (Affymetrix, Agilent, Ciphergen). **DNA chips** represent today the major type with **more than 83 % of sales**. Lab on chip is emerging – mostly with Caliper sales – and represents 10 % of the total. The remainder consists of protein chips (mostly Ciphergen) and other types of DNA arrays.

Biochip market in 2012



The medical devices market is estimated to be 170B Euro in 2003. The *in-vitro* diagnostics market was 20B in 2001 and 37B in 2010. The overall growth rate is 7% per annum with the major drivers being:

- Favourable demographics;
- Improvements in healthcare;
- Innovation and improvements in current technologies;

The per capita annual expenditure for health care is approximately \$3000 in the U.S., \$3200 in Germany, and \$ 2000, on average, in Europe. The total world market is estimated at \$ 2.8 trillion where individual segments include \$140 billion for medical instruments and \$400 billion for pharmaceuticals.

US companies account for more than 50 % of the total market (43% of the EU market). In some sectors such as cardiovascular the market share of US companies is even higher.

The market environment of the medical devices and diagnostics sector is changing: the markets have grown often rapidly in the last few years. Factors for this change vary across individual segments of the sector but common ones include improved sales, market growth, impact of new products and new technologies and price reduction. Likewise, key trends and developments vary but they include price sensitivity, healthcare budgetary constraints and increasing competition caused by mergers and company consolidation (e.g. Johnson and Johnson and De Puy, Boston Scientific and Schneider).

The sector responses to these changes are:

- Increased R&D spending;
- More rapid introduction of new products;
- Cost reduction in the supply chain;
- Increased flexibility;
- Moving to lower cost locations.

In the next 5 years a significant change in the market will be observed, primarily driven by:

- price pressure;
- continuing consolidation of companies within the sector;
- reduced product lifecycles leading to faster new product introduction;
- technology changes driven by small leading-edge companies;
- increased regulation.

Both the Diagnostics and Medical Device sectors have the similar needs and pressures; however, the diagnostics sector is smaller in terms of market size and number of companies.

Several remarks can be made on the above market analysis:

- it assumes business as usual: it is an incremental steady development and does not consider any breakthroughs in the markets;
- it does not tell who the players will be;
- one has to determine how the added value changes and who gets it.

4.2 Business issues

About value creation:

We have not yet seen any data that compares bio-microsystems to other diagnostic technologies. Evaluating this item is a rather complex task; for instance, what is the added value of a cell phone for the end user? A major factor in this case is the immediate availability at any nearby shop. There is a technological advantage, a cost advantage, but also the convenience of easy availability to the user. So while choosing a new application, one should look for the whole value chain and whether this application constitutes a real breakthrough.

Molecular Diagnostics value chain

Bio/marker knowledge & IPR	(Bio)content provider
Biomaterials (antibodies) & biochemical processing	Disposable
Microfluidics & detection	
Reader & signal processing	System/service provider; application & market access
System integration hospital (workflow) or e-health (home care) business	

Business models

In such a chain, added value sharing is not obvious now. In the long run, it might occur that only two players will be concerned, a technology provider and a service provider. As an indication of things to come, one can look at the acquisition of Amersham by General Electric. Expertise of GE in electronics and Amersham in the bio field enables a new enterprise that is able to generate both the content as well as the hardware. So they can capture the whole value chain because they have the bio content and the ability to make a large part of the platform. GE manufactures very complex medical instruments that are used in all hospitals. This is a very interesting and intriguing development that certainly affects the industry.

Will microelectronics be just a universal technology provider without any involvement in the biology layer? Will they systematically be involved with biology suppliers? What will be the marketing strategy?

A major issue in the markets (and how businesses will operate) is the role of the government and healthcare organizations. The reason why a lot of companies are moving to the United States is because there they can expect returns more easily than in Europe. Therefore, actions on hospitals, social security, complementary insurances, etc will be necessary in Europe.

Although the US is still a major player, it is also important to observe the emergence of other countries, in particular from Asia. In a market where small companies abound, it is conceivable that many of them will emerge from unexpected countries, in many cases facilitated by local regulations.

Intellectual property rights issues

IP rights play a very important role in the emerging bio-microsystems industry, with several companies pursuing aggressive positioning. Since the industry has been so far mostly venture-capital funded, with valuations based more on potential (often determined by patents) rather than actual businesses, little incentive has been present for cross-licensing and cooperative agreement.

As a result, frequent litigation has been the norm. Higher profile cases have included the Affymetrix vs. Oxford Gene Technology and the Nanogen vs. Combimatrix legal skirmishes, both now settled.

Our forecast is that the actual introduction of the first products in the market, and pressures coming from investors to settle pending litigation, will have an effect on the industry, with an increase in cross-licensing and agreement, but a level of litigation unusual to the semiconductors and electronics industry **is still** expected.

Some of the most relevant portfolios include:

- London-based OGT, which by now appears to be devoted mainly to the commercial exploitation of its IP base.
- Affymetrix, which has complemented its existing portfolio via acquisitions
- Nanogen, which has a number of relevant patents, the most interesting likely being those related to electronically assisted hybridisation.

On a separate note, we could mention the Roche PCR patents and alternative amplification systems, e.g. Becton Dickinson's SDA technology.

A large number of other players are also involved, almost all of them US-based, so that at the moment the only significant patent portfolio in Europe appears to be that of OGT. It is worthwhile mentioning that only research teams with a multidisciplinary approach have the ability to write strong patents at system and application level rather than at technology level only. The European weakness in this field of multidisciplinary organizations is limiting its ability to build a strong patent portfolio.

A business analysis centred on pros/cons

In order to identify the driving forces and roadblocks to large-scale marketing of bio-microsystems, market studies usually do not have much to add in situations of emerging technologies/markets. It is then useful to analyse the pros/cons for the mass production of bio-microsystems. We will concentrate on the medical market, the other ones (agriculture, environment and security) being more suitable to standard analysis. The key aspect is the occurrence (or lack thereof) of a major breakthrough in diagnostics and monitoring systems, implying multi-million sales for given devices.

The pro arguments

- Present research work confirms the need for parallelism, high speed, and functional integration. Bio-microsystems are indeed capable of it, but they cannot yet demonstrate a significant (and decisive) cost reduction in healthcare.
- However, it may well be that the most urgent needs are those related to the focused monitoring of chronic patients. This could employ tethered bio-microsystems, or through implants that would combine monitoring, stimulation and drug release.
- Low invasiveness means that patients will be able to carry out tests themselves. This may lead to new markets, such as systematic tests (associated to specific chronic diseases or preventative monitoring in certain age groups) to appear. Similarly, this could have an outstanding impact in the current trends of auto-medication. These markets do not exist today because such tools still do not exist, but they may be addressed by bio-microsystems.
- Timing is a big advantage.

DNA Array tests for Diagnosis: Translates into Lower Mortality, Less Time, Lower Cost

Conventional Process: Diagnosis: 3 days (Treatment: broad spectrum antibiotics) then revise therapy.

DNA Diagnostics: 0.5 to 1 hour then *targeted* antibiotic treatment begins *immediately*; this speed lowers total cost of diagnosis & improves therapy decisions. Detailed monitoring can be done on a daily basis.

- *niche markets:* here only the bio-microsystem could allow you to obtain a necessary profile with several hundred analytes. Unlike those situations where bio-microsystems are competing against more traditional techniques, exploring these markets can make a strong case for the establishment of bio-microsystems as a competitive technology in a broader scenario.
 - A good example is that of blood donation screening. Actually, in all developed countries blood transmitted infectious diseases testing is achieved by real-time PCR analysis in a (8-16 member) blood pool. In this way a number of viruses (HIV, HCV, HBC) can be easily detected. There is a real market and a real demand to make this blood testing more rapid, more sensitive, by moving from pool to single unit testing. The sensitivity issue is of paramount importance; low contamination is still difficult to detect in pool samples and ideally the test should be extended to a larger number of pathogens. This is a real need that is very difficult to address, but we can explore the use of microsystem-based multiplex PCR to achieve those objectives. Issues would include detection sensitivity, reliability, traceability requirements, etc. The other reason for this to be a good application is that the prescriber is also responsible for the costs. However, the blood donation is one of the fields of high regulation because of the consequences of an eventual contamination.
 - Defence against biological warfare. Following the announcement by ST Microelectronics of the prototype PCR chip a year ago, they got independent requests from various defence ministries. They all have their own ideas for developing a portable cDNA detection system with highly integrated devices. While the defence markets may never be large, they could be decisive in the development of the technology in its nascent phase, as occurred for microelectronics.

The con arguments

- Drug markets increase at a faster speed than diagnostics, which makes resources less available for bio-microsystems.
- These new technologies cannot by themselves create a huge new market. It's not so much a technology that drives a market than how many physicians prescribe how many tests. Something will happen to these technologies if we find the niches. We also need to satisfy the following criteria:
 1. Reliability of the assay, specificity, sensitivity, false negative and positive values percentage
 2. Easy automation
 3. Large product range (Investment for expensive equipment for manufacturing is impossible without significant product range).
- Medical practice still relies on more traditional methods. Following clinical examination, a patient is sent for laboratory tests and based on the results a given drug is prescribed. Decades ago it was predicted that home tests would revolutionise medicine, which did not happen. Despite isolated successes such as the home pregnancy test and urine dipstick tests for clinical use, there is resistance

against the introduction of such techniques even when the technology is sound, as it happened with the dipstick staphylococcus test twenty years ago.

- The massive generation of information, which is one of the strengths of bio-microsystems, is by itself also a problem. The value of such volume of information is in many cases arguable. Unless some intelligence is added to the system, allowing the information to be adequately processed, the usefulness of the data is questionable. Additionally, there are ethical and psychological issues to be considered as the patient has direct access to the information or it is made available outside the clinical setting.
- The medical community tends to resist against the introduction of certain new technologies, as was the case with information technology. However, if it is cost-effective to the social security system it may be seen differently.

4.3 Issues in bio-microsystem development

Time frames

As we can see thus far, the bio-microsystems industry is characterized by a typically long timeframe. Ideally we should find specific niches that will trigger the investment process and allow the industry to continue its expansion in other directions.

Market size is also of concern. In the early 80s it was thought that diagnostics would be a booming market, but twenty years later it is still around the mark of \$10B in sales, even with a growth rate of 30% a year and a growth expectancy of another 20 years.

We should expect that many biomedical applications will continue to be developed using other technologies and later transferred to a bio-microsystem platform. It remains to be seen how some of the major testing techniques will undergo this process (given that most of the biology development has already been done) and who will pay for it. There has been some progress at the research level, where genetic or protein profile analyses have been correlated with the clinical status of patients affected with multigenic or complex diseases. An interesting example is that of prostate cancer: current PSA testing cannot help differentiate between prostatitis and prostate cancer when the PSA result is in the low range. One team of the National Cancer Institute in the USA has demonstrated that an accurate diagnosis can be established upon protein profile analysis by mass spectrometry. While there is a lot of debate on the use of such an approach, the real question still is whether we can translate this genetic and/or protein profile analysis into real diagnostic tools.

Cultural issues between industries

Collaboration between electronics and pharmaceutical/diagnostic companies is difficult as a result of fundamental differences in IP policies, where the electronics industries tend to share and give licenses and the pharmaceutical/diagnostic companies tend to block and protect their areas of interest. In European projects participating of the FP6 framework this has already led to insurmountable difficulties and the withdrawal of at least one Integrated Project.

What is needed is a change or evolution of cultures, from autarchic to open cooperative companies. It will be a new type of business, mixing bio and micro, with very different cultures.

Standards

In the gene profiling there are rather well established procedures such as confocal microscopy, fluorescent detection. For proteins, the mechanisms will be completely different, requiring for instance choices of ligands and transducers. Overall the technology in the proteomics domain is comparatively poor.

There are not yet technologies that really answer existing needs. As we are still in the infancy phase of a new technology, when many technologies compete, it is difficult to progress, in particular as funding appears to have a very uncertain return. Conversely, how many technologies will survive to fulfil the various needs?

How will we reapply the same platform for several users and several bio-companies? Is it even reasonable to consider such a thing? How can we share a given technology between users? The customer (diagnostics labs, hospitals, doctors, patients) would also like to have the same platform for different applications/tests. One will also need to answer validation issues for specific applications (prostate cancer, IVD, AIDS, blood screening, etc).

How will we show/demonstrate the sensitivity, specificity, reproducibility, linearity, etc. before going to market? Even after that we will need the transition to the real product (packaging problems, handling etc).

One critical point when we contemplate the diagnostic field is that it is highly regulated. One has to demonstrate (to the FDA, as well as to the European regulatory authorities) that any new technology is sufficiently accurate and reliable. Additionally, the end users must be confident with the provided results. This can only be achieved by incorporating some internal controls and by implementing a right QC strategy (starting from the design phase up to the manufacturing step) to be sure that these new technologies or new devices have reached the required level of reliability.

Funding issues

We have observed the disappearance of venture capital in the starting phases, which in part is explained by the early demise of related technologies. At the moment in the US there is huge federal funding (through usual channels, plus the Department of Homeland Security). It creates a large funding imbalance, and distorts competition in an emerging field that cannot be self-funded. On the other hand, the fragmentation of the European market, the variety of social security systems and of national regulatory agencies makes it much more difficult for industries to operate in Europe.

Even though the defence/security needs may not create a mass market for devices (as did the space and defence systems of the 60s and 70s for microelectronics) they will create the technology base for the industry. The US government is driving the advancement of diagnostics devices in particular, because it is clearly advantageous to have standalone autonomous detection instruments.

Due to these factors, many European companies have already moved their research labs to the US, due to a number of converging factors: federal funding, large base for possible cooperation with well-equipped and staffed university labs, leading market in innovation; this inevitably gives US-based companies and start-ups a competitive advantage. In addition to federal funding opportunities, the healthcare market is very innovative and looking for cost-effective solutions; this means that newly introduced technologies in the US will stand a much higher chance of fast success and investment return.

University problems

One of the difficulties in universities is the structure of disciplines. How to hire a biologist in a physics department? How to get microfabrication skills in a biology department? The existence of interdisciplinary centres in the US, with a well-developed sense of teamwork and collaboration culture, makes it much easier to work in this field in the US. This type of culture is much needed in Europe at the moment and fortunately some changes are starting to happen; for instance, in some countries (such as Germany) it is now much easier to hire a biologist at a physics department.

What are then the educational issues? Do we need the creation of multidisciplinary courses? It seems that better results in R&D-orientated education can be achieved by having one major (biology, physics, chemistry) with minors (in the other fields) because for R&D work one needs advanced education in at least one discipline. In other industrial activities such as business development, strategic analysis and marketing a broader culture might be preferred.

A major development problem will be to bring industrial quality at the level of microelectronics: homogeneity, reproducibility, reliability. To that end, good facilities at universities will be needed to train people at the right level.

A unified patent law should be envisioned that allows for an efficient and timesaving procedure for information exchange between universities and industry. European universities usually cannot afford to sustain a powerful patent office. Universities are generally not in the position to negotiate IP issues with their industrial counterparts. Funding agencies should provide patent support, both financially as well as intellectually. Furthermore, there is a different understanding of IP value in industry and in academic labs. This can often kill collaborations. Education and confidence are needed there.

5. Conclusions

The field of bio-microsystems is certainly one that will continue to draw the attention of microelectronics, companies, European institutions, and healthcare organizations.

The issues are not simple to solve if one wants to have a competitive European industry in the future, in particular as Europe is having a late start, and has a number of drawbacks to become efficient.

The technology issues will not be easy to solve in view of the complex systems to implement, as well as specific aspects such as standards, regulations, and market access.

These points are presented in the executive summary and will not be reproduced here.